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Cheryl Liljestrand
Tanox Inc
10301 Stella Link
Houston, TX 77025-5497

EXAMINER	
HILL, KEVIN KAI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,326	YAO ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-52* is/are pending in the application.

4a) Of the above claim(s) *34-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on June 20, 2006 is acknowledged.

Applicant has elected the invention of Group I, Claims 31-33, drawn to a purified polypeptide comprising an amino acid sequence of SEQ ID NO:2, or a functional variant or fragment thereof.

2. Election of Applicant's invention(s) was made with traverse.

In the response filed March 12, 2007, May 22, 2007 and June 20, 2007, Applicant argues that the special technical feature of the invention is SEQ ID NO:2, and all claims relate to this special technical feature, wherein Chapter 10 "Unity of Invention" in the PCT Guidelines provides that a protein and its encoding nucleic acid have Unity, and the methods of manufacturing or using the protein have Unity.

Applicants' arguments have been fully considered but are not found persuasive.

As a first matter, Unity of Invention is lacking *a priori* because not all claims are directed to a polypeptide having the special technical feature of SEQ ID NO:2. Rather, polypeptide embodiments are claimed that do not require the special technical feature of SEQ ID NO:2, e.g. variants and derivatives of SEQ ID NO:2, wherein a claimed polypeptide is only required to have amino acids 43-150 of SEQ ID NO:2, thereby excluding the special technical features afforded by amino acids 1-42 and 151-270 of SEQ ID NO:2. It is noted that the claims embrace full-length SEQ ID NO:2 having the property of being an antagonist to the NFAT activating receptor ligand, thereby (apparently) inhibiting the action of the NFAT activating receptor (SEQ ID NO:2 itself). However, the working example in the specification (pg 22, Example 6) discloses that SEQ ID NO:2 possesses stimulatory activity and that over-expression of SEQ ID NO:2 activates NFAT. While the variant or fragment of SEQ ID NO:2 may have antagonistic functional properties, the results of full-length SEQ ID NO:2 are contradictory to the functional property presently claimed.

While Unity of Invention *may* [emphasis added] exist between a polypeptide and its encoding DNA, the prior art discloses (see below) the instantly claimed polypeptide of SEQ ID NO:2, and thus the special technical feature does not contribute over the prior art. Therefore, Unity of Invention is lacking between the claimed polypeptide and isolated nucleic acids encoding said polypeptide.

With respect to Unity of Invention regarding methods of making and/or using the claimed polypeptide of SEQ ID NO:2, no claims of making or using the polypeptide of SEQ ID NO:2 are recited. Rather, claims are recited to make an antibody using a polynucleotide encoding a polypeptide of SEQ ID NO:2, or variant or fragment thereof, for example. Furthermore, additional claims are drawn to the use of an antibody or a polynucleotide encoding a gene-silencing RNA, and these claims do not require the use of polypeptides comprising SEQ ID NO:2.

The polypeptide of SEQ ID NO:2 appears to be signal transducing receptor molecule. Applicant has not provided evidence demonstrating how an antibody that recognizes SEQ ID NO:2 has *the same* [emphasis added] special technical feature as the polypeptide of SEQ ID NO:2. The art recognizes that antibodies have biological properties that are distinctly different than the polypeptide antigen recognized by said antibody. Absent evidence to the contrary, the two distinctly different polypeptides have distinctly different special technical features.

Applicant has not demonstrated how the transgenic knockout animal comprising a disruption in the endogenous NFAT activating receptor gene or the antisense RNA has the same special technical feature of the polypeptide of SEQ ID NO:2. The transgenic knockout animal and the effects of the antisense RNA will have a phenotype caused by the *absence* [emphasis added] of the endogenous NFAT activating receptor; whereas, the special technical feature is the *presence* [emphasis added] of SEQ ID NO:2. Applicant has not provided evidence that the phenotype of said transgenic knockout animal or the antisense RNA is due *exclusively* [emphasis added] to the presence of the special technical feature of SEQ ID NO:2.

MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to polynucleotides encoding a polypeptide, polynucleotides encoding a gene-silencing RNA, antibodies and transgenic organisms, requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to an antibody would not be adequate to uncover prior art related to a gene-silencing RNA.

Further, a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claims including limitations to polypeptides excluding the special technical feature of SEQ ID NO:2, polynucleotides encoding said polypeptides, antibodies, gene-silencing RNAs and transgenic organisms in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 34-52 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 31-33 are under consideration.

Priority

5. This application is a 371 of PCT/US03/29643, filed on September 19, 2003. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/412,157, filed on September 19, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Specification

Sequence compliance

6. **This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).** However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers, specifically:

Page 19, [0101], lines 1-2,

Page 21, [0104], lines 1-2, and

Page 24, [0113], lines 10-13.

The sequences are not already present in the sequence listing filed March 13, 2005. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

7. **The disclosure is objected to because of the following informalities:**

The specification discloses a "novel nuclear factor....having the *amino* [emphasis added] sequence shown in SEQ ID NO:1" (pg 2, [0018]). However, SEQ ID NO:1 is a nucleic acid sequence.

The subject of the following sentence is missing: "These antagonistic _____ [peptides?] block the binding of the natural ligand for NFAT activating receptors by binding to the ligand and preventing the ligand from binding to the native receptor." (pg 6, [0041], line 4)

Appropriate correction is required.

Claim Objections

8. **Claims 32-33 are objected to because of the following informalities:**

With respect to claim 32, the claim recites dependency on cancelled claim 1. In the interest of compact prosecution, the Examiner interprets Claim 32 to be dependent on Claim 31.

With respect to claims 32-33, these claims each identify NFAT as a receptor whose activity is targeted in the claimed invention. However, the claims do not first identify the receptor by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF).

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. **Claims 31-33 are rejected under 35 U.S.C. 101** because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

According to the Revised Utility Examination Guidelines (see the Federal Register, Vol. 66, No. 4, pp. 19092-1099; January 5, 2001; also available at http://uspto.nov/web.menu.utility.pdf) the following definitions of credible, specific, and substantial apply.

The claims are drawn to a genus of polypeptides comprising the amino acid sequence of SEQ ID NO:2, or a variant or fragment thereof, wherein said polypeptide possesses the functional property of antagonizing the NFAT activating receptor ligand via specific binding, thereby inhibiting the activation of the NFAT activating receptor.

Specific Utility

A "specific utility" is specific to the subject matter claimed and can "provide a well-defined and particular benefit to the public." *In re Fisher*, 421 F.3d 1365, 1371, 76 USPQ2d 1225, 1230 (Fed. Cir. 2005). This contrasts with a *general* [emphasis added] utility that would be applicable to the broad class of the invention.

In the instant case, the purified polypeptides of the present invention are preferably NFAT activating receptors involved in the transcriptional regulation of various cytokine and cellular receptor genes (pg 6, [0039]). In another aspect, the present invention provides agonists and antagonists that specifically bind to NFAT activating receptors and inhibit or activate the expression or action of the receptors, wherein antagonists are a soluble form of NFAT activating receptors, with preferred embodiments of those peptides selected from the group consisting of amino acids 43-150 of SEQ ID NO:2. These antagonistic peptides block the binding of the natural ligand for NFAT activating receptors by binding to the ligand and preventing the ligand from binding to the native receptor (pg 6, [0040-0041]). The agonists and antagonists are used for the treatment of various immune diseases (pg 6, [0044]; pg 16, [0087]) or for making antibodies (pg 7, [0045]).

It is noted that the NFAT receptor ligand, for which the polypeptides comprising SEQ ID NO:2, or variants or fragments thereof, are claimed to functionally antagonize to the effect of therapeutic value, is undisclosed. Thus, it appears the instant polypeptide of SEQ ID NO:2 is an orphan receptor whose stimulatory ligand is neither known in the prior art nor disclosed in the instant specification.

Thus, the asserted utilities are not considered "specific" utilities because they are not specific to SEQ ID NO:2.

Substantial Utility

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility. See also MPEP 2107-2107.02, and *Brenner Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

"[A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the substantial utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230.

In the instant case, the specification discloses that there exists a continuing need to understand the NFAT pathway and to use this understanding to develop compositions and methods useful to modulate the pathway, including agonists and antagonists such as antibodies that regulate cytokine and cell surface receptor expression and screening methods that are useful to identify drugs that prevent or treat cytokine and receptor related disease (pg 2, [0005]).

However, neither the specification nor any art of record teaches what SEQ ID NO:2 is, what it does, a utility for any of the variants or fragments claimed, any relationship to a specific disease, or establish any involvement in the etiology for a specific disease. Further experimentation is required to determine what the use is for SEQ ID NO:2 and any variant or fragment thereof. There is no evidence of record that a SEQ ID NO:2, or a variant or fragment thereof possesses the essential feature of the invention, namely antagonizing NFAT activating receptor ligand via specific binding.

While methods of researching the function of SEQ ID NO:2 and any role the polypeptide has in disease etiology and pathology is of value to the scientific and medical arts, this use is not considered a specific, substantial or practical utility because it does not provide some "real-world" value or immediate benefit to the public. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Basic research, such as studying the properties of the claimed product itself, e.g. the polypeptide of SEQ ID NO:2, or the mechanisms in which the polypeptide, agonist or antagonist thereof is involved, does not define "substantial utilities". Labels such as "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

10. **Claims 31-33 are also rejected under 35 U.S.C. 112, first paragraph**. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or

a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. (see below)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. **Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a polypeptide comprising an amino acid sequence of SEQ ID NO:2. At issue for the purpose of written description requirements is the absence of support for the genus of functional variants of SEQ ID NO:2, wherein said functional variants are claimed to possess the property of being an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure.

In the instant case, SEQ ID NO:2 and Tyrosine-mutated variants (Y1A, Y2A and Y12A) in the ITAM motif (pg 24, Example 7) and are the only species whose complete structure is disclosed (pg 21, [0105], Example 4).

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the functional variant or fragment has either has the same or similar biological function as its native counterpart or does not have the same or similar biological function as its native counterpart but is useful as an immunogen. It is noted that the claims embrace full-length SEQ ID NO:2 having the property of being an antagonist to the NFAT activating receptor ligand, thereby (apparently) inhibiting the action of the NFAT activating receptor (SEQ ID NO:2 itself). However, the working example in the specification (pg 22, Example 6) discloses that SEQ ID NO:2 possesses stimulatory activity and that over-expression of SEQ ID NO:2 activates NFAT. While the variant or fragment of SEQ ID NO:2 may have antagonistic functional properties, the results of full-length SEQ ID NO:2 are contradictory to the functional property presently claimed.

The specification does not disclose any identifying characteristic as to how an artisan would have differentiated any one variant or fragment from another. The variant differs from its native counterpart by one or more amino acids, including modifications, substitutions, insertions, and deletions, and, wherein a fragment would retain any biological activity of its native (full-length) counterpart (pg 4, [0025], lines 1-3; [0027], lines 1-2). It is noted that all these variants and fragments of SEQ ID NO:2 vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The applicant has not provided any description or reduction to practice of the enormous genus of variants and fragments of SEQ ID NO:2, wherein said variants and fragments possess the property of being an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor. The specification and claim(s) do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim(s) do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO:2. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the polypeptide sequences possessing the functional property of being an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor as defined by the specification or encompassed by the claims. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:2 and tyrosine-mutated ITAM motif variants (Y1A, Y2A and Y12A) are not representative of the genus because the genus is highly variant and none of these polypeptides are disclosed as having the claimed functional properties. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of polypeptide variants and fragments of SEQ ID NO:2 having an essential feature of the invention, namely possessing the functional property of being an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

12. **Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a polypeptide consisting of the amino acid sequence of SEQ ID NO:2, does not reasonably provide enablement for an enormous genus of polypeptides comprising the amino acid sequence of SEQ ID NO:2, or a variant or fragment of SEQ ID NO:2, wherein said variant or fragment possesses the functional property of being an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

Due to the open language "comprising" of claims 31-33, the breadth of the claims is broad for encompassing a polypeptide "comprising" an amino acid sequence, variant or fragment of SEQ ID NO:2, wherein unknown sequences are attached to a fragment of any size of SEQ ID NO:2.

The inventive concept in the instant application is the *in silico* identification and cloning of a hypothetical protein having the amino acid sequence of SEQ ID NO:2 (pg 19, [0100]), wherein the polypeptide comprises an extracellular immunoglobulin (Ig) domain, a transmembrane region, and an intracellular immunoreceptor tyrosine-based activation motif (ITAM), indicating that the hypothetical protein may be an NFAT activating receptor family member. Applicant contemplates that soluble forms of SEQ ID NO:2, and/or variants or fragments thereof may be useful as a competitive inhibitor of the NFAT receptor ligand, thereby abrogating activation of the endogenous NFAT receptor. These contemplated NFAT receptor ligand antagonists are contemplated to be useful in methods for preventing or treating NFAT protein-mediated diseases in a mammal (pg 16, [0087]).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The claimed SEQ ID NO:2 variants differs from its native counterpart by one or more amino acids, including modifications, substitutions, insertions, and deletions, and, wherein a fragment would retain any biological activity of its native (full-length) counterpart (pg 4, [0025], lines 1-3; [0027], lines 1-2). Thus, the specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification do not place any limit on the number of amino acids that could be substituted.

Furthermore, the specification discloses that the functional variant or fragment of SEQ ID NO:2 has either has the same or similar biological function as its native counterpart or does not have the same or similar biological function as its native counterpart (pg 4, [0025]). The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution,

or which amino acids could be deleted or inserted so that the claimed polypeptide could function intentionally, either as the same as the non-mutant, native counterpart or differently from the non-mutant, native counterpart as contemplated. No consensus sequence for the claimed polypeptides is disclosed in the specification for any functional parameter.

It is noted that the NFAT receptor ligand, for which the polypeptides are claimed to functionally antagonize to the effect of therapeutic value, is undisclosed. Thus, it appears the instant polypeptide of SEQ ID NO:2 is an orphan receptor whose stimulatory ligand is neither known in the prior art nor disclosed in the instant specification.

It is also noted that the claims embrace full-length SEQ ID NO:2 having the property of being an antagonist to the NFAT activating receptor ligand, thereby (apparently) inhibiting the action of the NFAT activating receptor (SEQ ID NO:2 itself). However, the working example in the specification (pg 22, Example 6) discloses that SEQ ID NO:2 possesses stimulatory activity and that over-expression of SEQ ID NO:2 activates NFAT. These results are contradictory to the functional property presently being claimed.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the variants of SEQ ID NO:2 would have properties related to that of SEQ ID NO:2. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science 247: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, pg.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's

sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, pg.1306). The three-dimensional folding of the native molecule however is of significant importance in an antibody response, because epitopes of an antibody could be linear and/or conformational. For example, Roger et al (Bioscience Reports, 8(4): 359-368, 1988) teach that several epitopes of p85 glycoprotein are conformational determinants and are destroyed by reduction of said glycoprotein (abstract). The references thus demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the characteristics or three dimensional structure of a protein, and consequently the binding and characteristics of the antibodies specific for said protein.

Similarly, one cannot predict the effect of the attached sequences with unknown structure on the conformation of the claimed fragment, because the amino acids of a sequence influence its conformation (Bowie et al, 1990, supra). For example, one cannot predict whether the peptide fragment of SEQ ID NO:2 is even exposed on the surface of the protein with attached unknown sequences for its binding to an unknown and undisclosed NFAT receptor ligand.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the enormous genus of polypeptides comprising an amino acid sequence of SEQ ID NO:2, or a variant or fragment thereof will possess the functional property of antagonizing the NFAT receptor ligand, and it would be undue experimentation for one of skill in the art to screen for the claimed variants.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must

supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo NordiskA/S* 42 USPQ2d 1001, at 1005). The claimed polypeptides comprising an amino acid sequence of SEQ ID NO:2, or a variant or fragment thereof, wherein said polypeptides possess the functional property of antagonizing the NFAT receptor ligand constitute such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel.* In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a polypeptide consisting of the amino acid sequence of SEQ ID NO:2, is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. **Claims 31-33 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "the receptor" in reference to the antagonistic/inhibitory function of the polypeptide of SEQ ID NO:2, or variant or fragment thereof recited in Claim 31. There is insufficient antecedent basis for this limitation in the claim. Furthermore, it is unclear if the polypeptide of SEQ ID NO:2, or variant or fragment thereof recited in Claims 31 and 33 being claimed to antagonize/inhibit the function of the NFAT activating receptor, which is SEQ

ID NO:2, or the NFAT activating receptor ligand, because the binding of a peptide variant or fragment of SEQ ID NO:2 to the NFAT receptor ligand connotes that the NFAT receptor ligand is a receptor for the peptide variant or fragment of SEQ ID NO:2.

Correction and/or clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. **Claims 31-33 are rejected under 35 U.S.C. 102(e)** as being anticipated by Yang et al (WO 03/016506).

Yang et al disclose a polypeptide having 100% sequence identity with the instantly claimed polypeptide having the amino acid sequence of SEQ ID NO:2. (pg 104, Incyte polypeptide ID 8001939CD1, SEQ ID NO:25; Search Result provided).

Yang et al do not teach the polypeptide to be an antagonist that specifically binds to NFAT activating receptor ligand and inhibit the action of the receptor. It is noted that the claims

embrace full-length SEQ ID NO:2 having the property of being an antagonist to the NFAT activating receptor ligand, thereby (apparently) inhibiting the action of the NFAT activating receptor (SEQ ID NO:2 itself). However, the working example in the specification (pg 22, Example 6) discloses that SEQ ID NO:2 possesses stimulatory activity and that over-expression of SEQ ID NO:2 activates NFAT. The results of full-length SEQ ID NO:2 are contradictory to the functional property presently claimed.

The biological properties are considered to be an inherent feature of the polypeptide. Thus, the polypeptide of SEQ ID NO:25 of Yang et al fulfills the instantly recited functional limitations because it has the identical amino acid sequence presently claimed.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kevin K. Hill

Q. JANICE LI, M.D.
PRIMARY EXAMINER